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Prognostic factors for survival in metastatic breast cancer by hormone receptor status

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Abstract Hormone receptor (HR) status is an important prognostic factor for patients with metastatic breast cancer (MBC) and is also correlated with other prognostic factors, such as initial lymph node status, HER2-Neu status and age. The prognostic value of these other factors, however, is unknown when stratified by HR positive versus HR negative patients. The aim of this study was to evaluate prognostic factors for MBC survival in relation to HR status. Dutch women diagnosed with breast cancer in 2003–2006 treated with curative intent who developed MBC within 5 years of follow-up were selected from the Netherlands cancer registry ($N = 2{,}001$). Independent prognostic factors for survival after metastatic occurrence were determined by multivariable Cox survival analyses stratified by HR status. Interactions between HR status and prognostic factors were determined. Median survival for MBC patients with HR negative (HR−) tumours was 8 months, compared to 19 months for HR positive (HR+) patients. The prognostic value of lymph node status, HER2-Neu status, adjuvant endocrine treatment and first-line palliative chemotherapy was dependent on HR status. Initial lymph node status was independently associated with survival in HR− patients, but not in HR+ patients. HER2-Neu positive status was associated with better survival in both HR+ and HR− patients, although the association was stronger in HR− patients. Similarly, patients treated with first-line palliative chemotherapy fared better, especially HR− patients. HR+ patients had worse survival if they had received adjuvant endocrine treatment. This study shows that the prognostic value of various factors depends on HR status in MBC. This information may help physicians to determine individual prognostic profiles and therapeutic strategies for MBC patients.

Keywords Metastatic breast cancer · Prognostic factors · Hormone receptor status · Survival

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Background

Metastatic breast cancer (MBC) is generally considered an incurable disease. Although prognosis has improved during the last two decades [1, 2], median survival is still limited at 18–30 months [3, 4]. Actual survival for individual patients varies widely, from just a few months to many years. A small subset of about 5 % of patients achieves long-term survival of over 10 years. Several prognostic factors have been identified in patients with MBC. A negative hormone receptor (HR) status of the primary tumour, a short metastatic-free interval (MFI), high histological grade, large tumour size, positive lymph nodes and older age are all associated with poor survival and metastases to the bones and soft tissue are associated with better survival [3–8]. Many of these prognostic factors are related to HR status. Compared to HR negative (HR−) tumours, HR positive (HR+) tumours often develop in older patients, have a longer MFI, are more likely to be low grade and have a tendency to metastasize to bone, rather than to visceral organs [7]. Whether the prognostic value of the respective factors is similar in patients with HR+ and HR− tumours is uncertain.

Mainly due to their small sample size, previous studies on prognostic factors for MBC have rarely studied the interaction between the factors. Only Largillier et al. found a different prognostic effect for initial tumour size between HR+ and HR− tumours, with size being related to a poor outcome in HR−, but not in HR+ tumours. The aim of the present study was, therefore, to evaluate prognostic factors for survival in relation to HR status in MBC.

Patients and methods

Patients were selected from the nationwide population-based Netherlands Cancer Registry, which registers data about all newly diagnosed in situ and invasive tumours since 1989. Trained registration clerks extract information on patient characteristics, tumour characteristics, treatment and follow-up directly from patient files. Tumour sites and histology were coded according to the International Classification of Diseases for Oncology (ICD-O) [9], and staging according to the tumour, node and metastasis system (TNM) classification [10]. Hormone receptor status has been registered since the beginning of 2003, with tumours with at least 10 % positive tumour cells for oestrogen receptor (ER) or progesterone receptor (PR) defined as having a positive receptor status: ER+ and/or PR+, respectively. Her2–Neu expression has been registered since the beginning of 2005 and considered positive in case of Her2–Neu 3+ (strong and complete membranous expression in >30 % of tumour cells) or Her2–Neu 2+ (weak complete membranous expression in >10 % of tumour cells) confirmed with positive in situ hybridization (ISH).

Women diagnosed with primary invasive breast cancer (pT stage 1–3) between 2003 and 2006, without evidence of distant metastasis at the time of initial diagnosis and treated with curative intent, were included in this study ($N = 31{,}438$). Follow-up data were not available for patients who received neo-adjuvant systemic therapy ($N = 1{,}701$) and were, therefore, excluded. Women who had an ER− and PR+ tumour ($N = 249$), or who were not tumour free after initial treatment ($N = 104$), were also excluded from this study. Information on the occurrence of recurrent MBC within five years after diagnosis was derived retrospectively from the patients' files. For this study, only the first metastatic site was taken into consideration. Sites were categorized into six groups: liver, lung, bones, central nervous system (CNS), multiple sites, or other. Of the selected breast cancer patients, 2,668 developed MBC during the first 5 years of follow-up since diagnosis. In the end, 2,001 patients remained available for analysis, of whom 1,292 (65 %) had a HR+ tumour.

Statistical analyses

Patient and tumour characteristics are reported as frequencies and compared using χ^2 tests. Metastatic survival was defined as time between the date of diagnosis of MBC and the date of death, or the end of the study period (31 December 2012). Univariable survival analyses were performed by constructing Kaplan–Meier plots using the log-rank test for comparisons. Multivariable proportional hazard regression modelling was used to assess independent prognostic factors for survival. The analyses were also performed stratified on HR status. The prognostic factors in the multivariable model were selected based on statistical significance in univariable analyses ($P < 0.1$). With regard to the primary tumour, the following variables were examined: histological type, grade, tumour size, axillary lymph node status and HER2-Neu status according to pathology, surgery and adjuvant radiotherapy, endocrine and chemotherapy. In addition, the following MBC-related treatment variables were included: MFI, site of distant metastasis, age at MBC diagnosis, surgery, first-line palliative radiotherapy, chemotherapy and endocrine treatment (Table 1). Only adjuvant and first-line palliative treatment were available for analyses. Interaction between HR status and other prognostic factors was tested. Hazards in different subgroups of variables were tested for proportionality using graphical tools (Kaplan–Meier and Hazard plots) and the Schoenfeld residuals test.

A P value of <0.05 was considered to be statistically significant. Analyses were performed using STATA version 1.

Table 1 Patient and tumour characteristics by hormone receptor status

Primary tumour	HR negative		HR positive		*P*	Total		*Metastasis*	HR negative		HR positive		*P*	Total	
	N	%	*N*	%		*N*	%		*N*	%	*N*	%		*N*	%
Total	709	35.4	1,292	64.6		2,001	100								
Year of diagnosis					0.217										
2003	139	19.6	213	16.5				Metastatic free interval					<0.001		
2004	209	29.5	371	28.7		352	17.6	≤24 months	430	60.7	442	34.1		872	43.6
2005	211	29.8	397	30.7		580	29.0	>24 months	279	39.4	850	65.9		1,129	56.4
2006	150	21.2	311	24.1		608	30.4	Site					<0.001		
Histologic type					<0.001	461	23.0	Bones	95	13.4	515	39.9		602	30.4
Ductal	639	90.1	1,029	79.6				Multiple sites	279	39.4	385	29.8		658	33.2
Lobular	24	3.4	189	14.6		1,668	83.4	Liver	95	13.4	159	12.3		251	12.7
Mixed and other	46	6.5	74	5.7		213	10.6	Lung	105	14.8	97	7.5		201	10.2
Grade±					<0.001	120	6.0	CNS	68	9.6	37	2.9		105	5.3
I	12	1.7	116	9.0		128	6.4	Other	67	9.5	99	7.7		164	8.3
II	133	18.8	133	45.2		717	35.8	Age at metastatic diagnosis					<0.001		
III	532	75.0	509	39.4		1041	52.0	<50 year	224	31.6	286	22.1		510	25.5
Unknown	32	4.5	83	6.4		115	5.8	50–69 year	320	45.1	621	48.1		941	47.0
Tumour size					0.001			≥70 year	165	23.3	385	39.8		550	27.5
≤2 cm	224	31.6	510	39.5		734	36.7	Median (range)	57	25–94	61	24–93		60	24–94
>2 and ≤ 5 cm	411	58.0	691	53.5		1,102	55.1	Surgery					0.006		
>5 cm	71	10.0	86	6.7		157	7.9	No	614	86.6	1,178	91.2		1,792	89.6
Unknown	3	0.4	5	0.4		8	0.4	Yes	43	6.1	54	4.2		97	4.9
Lymph node status					0.684			Unknown	52	7.3	60	4.6		112	5.6
Negative	248	35.0	470	36.4		718	35.9	Radiotherapy					0.001		
1–3 positive	209	29.5	395	30.6		604	30.2	No	480	67.7	820	63.5		1,300	65.0
>3 positive	249	35.1	420	32.5		669	33.4	Yes	177	25.0	412	31.9		589	29.4
Unknown	3	0.4	7	0.5		10	0.5	Unknown	52	7.3	60	4.6		112	5.6
Her2-Neu					0.001			Chemotherapy					<0.001		
Negative	253	35.7	551	42.7		804	40.2	No	232	32.7	788	61.0		1,020	51.0
Positive	86	12.1	103	8.0		189	9.5	Yes	425	59.9	444	34.4		869	43.4
Unknown	370	52.2	638	49.4		1,008	50.4	Unknown	52	7.3	60	4.6		112	5.6
Multifocal					0.240			Endocrine treatment					<0.001		
No	519	73.2	907	70.2		1,409	17.1	No	636	89.7	600	46.4		1,236	61.8
Yes	126	17.8	240	18.6		364	18.4	Yes	21	3.0	632	48.9		653	32.6
Unknown	64	9.0	145	11.2		208	10.5	Unknown	52	7.3	60	4.6		112	5.6

Table 1 continued

Primary tumour	HR negative		HR positive		*P*	Total		*Metastasis*	HR negative		HR positive		*P*	Total	
	N	%	*N*	%		*N*	%		*N*	%	*N*	%		*N*	%
Surgery + radiotherapy					0.114			Hospital type					0.292		
BCS +RT	251	35.4	519	40.2		770	38.5	Academic	31	4.4	58	4.5		89	4.5
BCS −RT	8	1.1	11	0.9		19	1.0	Top clinical hospital	138	19.5	256	19.8		394	19.7
Amputation +RT	206	29.1	343	26.6		546	27.4	Other	204	8.8	422	32.7		626	31.3
Amputation −RT	244	34.4	419	32.4		662	33.4	Unknown	336	47.4	556	43.0		892	44.6
Chemotherapy					<0.001			Hospital volume per year					0.374		
No	230	32.4	726	56.2		956	47.8	<50	29	4.1	46	3.6		75	3.8
Yes	479	67.6	566	43.8		1,045	52.2	50–100	165	23.3	341	26.4		506	25.3
Endocrine treatment					<0.001			100–150	129	18.2	258	20.0		387	19.3
No	692	97.6	402	31.1		1,094	54.7	>150	51	7.2	91	7.0		142	7.1
Yes	17	2.4	890	68.9		907	45.3	Unknown	335	47.3	556	43.0		891	44.5

* *HR* hormone receptor, ± *low grade* grade I and II, *high grade* grade III, ≠ *BCS* breast conserving surgery, ¥ *RT* radiotherapy

Results

Characteristics

A total of 2,001 breast cancer patients who developed metastatic disease during the first 5 years of follow-up after treatment of primary breast cancer were analysed in this study. Table 1 summarizes the patient and tumour characteristics by HR status. Patients with HR+ tumours ($N = 1{,}292$, 65 % of total) were more likely to present with lobular carcinoma, low to intermediate grade, small tumour size (≤2 cm), HER2-Neu negative status, had a longer MFI (>24 months) and were older and more likely to present with bone metastases compared to patients with a HR− tumour ($P < 0.001$). Of the patients with a HR− tumour, a greater proportion had received adjuvant or first-line palliative chemotherapy ($P < 0.001$).

Survival

We observed 1,627 deaths among 2,001 patients. The median survival after MBC diagnosis was 14 months, 8 months in HR− patients and 19 months in HR+ patients ($P < 0.001$, Fig. 1). Table 2 shows the hazard ratios for MBC survival for the total group and by HR status. A positive HR status, longer MFI (>24 months), low grade, younger age, positive HER2-Neu status, bone metastases, surgery for MBC and first-line palliative systemic treatment were all found to be significant positive prognostic factors for survival in the total group. Significant interaction was found between HR status and lymph nodes, HER2-Neu status, adjuvant endocrine treatment and first-line palliative chemotherapy. Stratified analyses showed that, among the HR− patients, those with 1–3 positive nodes had a significantly poorer survival than those without

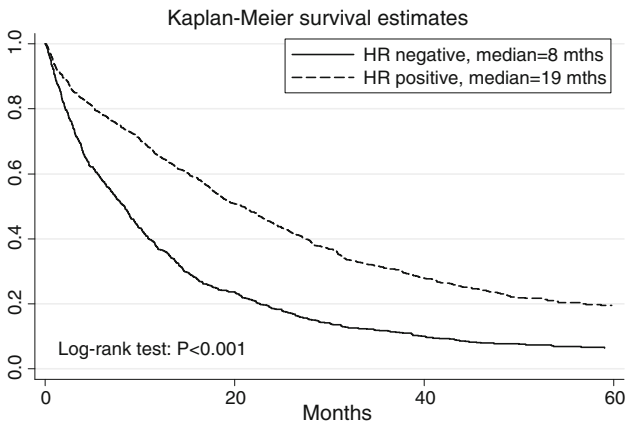

Fig. 1 Kaplan-Meier survival curve by hormone receptor (HR) status

Table 2 Multivariable cox regression analyses by hormone receptor status

	All			HR negative			HR positive			P^{∞}
	HR	95 % CI	*P*	HR	95 % CI	*P*	HR	95 % CI	*P*	
Primary tumour										
HR status										
Negative	Ref									
Positive	0.65	0.54–0.77	<0.001							
Grade$^{\pm}$										0.855
I	0.82	0.64–1.04	0.101	0.93	0.48–1.82	0.839	0.82	0.64–1.06	0.136	
II	Ref			Ref			Ref			
III	1.44	1.28–1.63	<0.001	1.21	0.95–1.53	0.115	1.43	1.23–1.66	<0.001	
Unknown	1.10	0.88–1.38	0.414	0.86	0.55–1.33	0.502	1.10	0.84–1.45	0.484	
Histologic type										
Ductal	Ref			Ref			Ref			0.059
Lobular	1.11	0.94–1.32	0.253	0.68	0.41–1.12	0.130	1.16	0.96–1.40	0.142	
Mixed and other	1.17	0.94–1.43	0.175	1.44	1.05–1.98	0.023	0.96	0.71–1.28	0.758	
Tumour size										
≤2 cm	Ref			Ref			Ref			0.686
>2 and ≤5 cm	1.10	0.98–1.23	0.098	1.15	0.95–1.38	0.164	1.01	0.86–1.17	0.870	
>5 cm	0.99	0.81–1.24	0.959	1.10	0.80–1.51	0.573	1.00	0.77–1.39	0.994	
Unknown	0.82	0.39–1.76	0.611	1.10	0.34–3.58	0.880	1.00	0.38–2.80	0.987	
Lymph node status										
Negative	Ref			Ref			Ref			<0.001
1–3 positive	1.06	0.92–1.21	0.368	1.42	1.16–1.74	0.001	0.87	0.73–1.05	0.144	
>3 positive	1.17	1.00–1.38	0.054	1.03	0.80–1.33	0.816	1.24	1.00–1.55	0.054	
Unknown	0.68	0.32–1.48	0.340	2.61	0.80–8.48	0.111	0.41	0.15–1.15	0.090	
Her2-Neu										
Negative	Ref			Ref			Ref			0.016
Positive	0.71	0.59–0.87	0.001	0.57	0.44–0.76	<0.001	0.82	0.62–1.06	0.127	
Unknown	1.42	1.09–1.86	0.009	1.52	0.94–2.45	0.086	1.40	1.01–1.95	0.044	
Surgery + radiotherapy										
BCS$^{\neq}$+RT$^{¥}$	Ref			Ref			Ref			0.238
BCS −RT	1.38	0.84–2.26	0.198	1.11	0.53–2.31	0.783	1.86	0.94–3.68	0.075	
Amputation +RT	1.06	0.91–1.23	0.481	1.08	0.81–1.37	0.588	1.05	0.86–1.27	0.656	
Amputation −RT	1.10	0.97–1.24	0.144	0.82	0.66–1.00	0.064	1.30	1.11–1.52	0.001	
Chemotherapy										
No	Ref			Ref			Ref			0.373
Yes	1.04	0.90–1.21	0.556	1.04	0.81–1.33	0.695	1.00	0.83–1.21	0.992	

Table 2 continued

	All			HR negative			HR positive			P^{∞}
	HR	95 % CI	*P*	HR	95 % CI	*P*	HR	95 % CI	*P*	
Endocrine treatment										
No	Ref			Ref			Ref			0.021
Yes	1.08	0.92–1.27	0.348	0.57	0.33–0.99	0.042	1.26	1.05–1.52	0.015	
Metastases										
Metastatic free interval										
≤24 months	Ref	–		Ref			Ref			0.098
>24 months	0.73	0.66–0.81	<0.001	0.60	0.50–0.71	<0.001	0.79	0.69–0.91	0.001	
Site										
Bones	Ref			Ref			Ref			0.198
Multiple sites	2.13	1.85–2.45	<0.001	2.88	2.18–3.82	<0.001	1.79	1.51–2.13	<0.001	
Liver	1.86	1.55–2.24	<0.001	2.09	1.49–2.92	<0.001	1.84	1.46–2.32	<0.001	
Lung	1.43	1.17–1.73	<0.001	1.56	1.12–2.17	0.008	1.26	0.96–1.65	0.103	
CNS	1.76	1.37–2.27	<0.001	1.53	1.04–2.24	0.031	1.88	1.26–2.81	0.001	
Other	1.04	0.84–1.29	0.733	1.12	0.77–1.63	0.551	1.12	0.84–1.48	0.434	
Age at metastatic diagnosis										
<50 year	Ref			Ref			Ref			0.079
50–69 year	1.23	1.08–1.40	0.002	1.14	0.93–1.36	0.183	1.42	1.18–1.68	<0.001	
≥70 year	1.95	1.63–2.32	<0.001	1.65	1.23–2.21	0.001	2.42	1.91–3.07	<0.001	
Surgery for MBC$^{\beta}$										
No	Ref			Ref			Ref			0.170
Yes	0.41	0.31–0.54	0.000	0.36	0.24–0.52	<0.001	0.39	0.25–0.56	<0.001	
Unknown	0.82	0.64–1.03	0.091	0.74	0.51–1.03	0.086	0.76	0.55–1.16	0.135	
Radiotherapy for MBC$^{\beta}$										
No	Ref			Ref			Ref			0.222
Yes	0.92	0.81–1.05	0.215	0.79	0.63–0.98	0.044	0.99	0.85–1.17	0.931	
Chemotherapy for MBC$^{\beta}$										
No	Ref			Ref			Ref			<0.001
Yes	0.54	0.46–0.61	<0.001	0.31	0.24–0.38	<0.001	0.76	0.64–0.92	0.002	
Endocrine treatment for MBC$^{\beta}$										
No	Ref			Ref			Ref			0.137
Yes	0.52	0.45–0.60	<0.001	0.61	0.37–1.01	0.054	0.55	0.47–0.64	<0.001	

* *HR* hormone receptor, $^{\infty}$ *P* p value for interaction, $^{\pm}$ *low grade* grade I and II, *high grade* grade III, $^{\neq}$ *BCS* breast conserving surgery, $^{¥}$ *RT* radiotherapy, $^{\beta}$ *MBC* metastatic breast cancer

positive nodes (HR = 1.42; 95 % CI = 1.16–1.74), whereas no poorer survival for this subgroup was observed among the HR+ patients (HR = 0.87; 95 % CI = 0.73–1.05). Better survival for HER2-Neu positive compared to HER2-Neu negative patients was much more prominent for the patients with HR− tumours (HR = 0.57; 95 % CI = 0.44–0.76) than among those with HR+ tumours (HR = 0.82; 95 % CI = 0.62–1.06). For HR+ patients, the use of adjuvant endocrine treatment was associated with a worse survival (HR = 1.26; 95 % CI = 1.05–1.52). The use of first-line palliative chemotherapy was associated with a better survival in HR− patients (HR = 0.31; 95 % CI = 0.24–0.38) but was less prominent in HR+ patients (HR = 0.76; 95 % CI = 0.64–0.92).

Discussion

This population-based study of 2,001 breast cancer patients who developed MBC during the first 5 years of follow-up shows that the prognostic value of lymph node status, HER2-Neu status, adjuvant endocrine treatment and first-line palliative chemotherapy is different for HR− and HR+ tumours. There was a median survival of 14 months for the whole group of patients, and we found that HR status, MFI, grade, HER2 status, site of metastasis, age and surgical and first-line palliative systemic therapy were statistically significant prognostic factors for overall survival.

Given the relatively short MFI of at most 5 years, the current study population represents an aggressive subgroup of MBC patients. Several earlier studies reported that MFI is a significant prognostic factor, with patients who develop metastatic disease more than 5 years after the primary tumour having a significantly better prognosis than those developing metastases within 5 years [3–5, 7]. The worst survival rates were for patients with MFI's shorter than 2 years [5, 7]. Largillier et al. [4], however, reported no significant relation between MFI and survival in multivariable analyses, either for the whole group nor after stratification for HR status.

As in earlier studies, we found that HR status is a prognostic factor for survival [3–5]. Although the median survival of 19 months for HR+ patients is substantially better than the 8 months for HR− patients, it remains rather poor. We found that the lymph node status of the primary tumour is not a significant prognostic factor for the group of patients with MBC as a whole. However, when analysed on HR status, we found a significantly poorer survival for patients with 1–3 positive lymph nodes among patients with a HR− tumour compared to those with negative lymph nodes. Literature results about the prognostic effect of lymph node status vary, with some reporting that the number of lymph nodes involved is associated with reduced survival [3, 5, 7], and others, like Largillier et al. [4], finding no significant relation between lymph node status and survival, neither after stratification on HR status.

Histological grade of the primary tumour has been shown to be an important prognostic factor in patients with MBC, higher grade being associated with worse survival [4, 11]. In our study, lack of statistical interaction indicated that the prognostic effect of histological grade was independent of the HR status of the tumour.

The HER2-Neu status of the primary tumour has been established as an important prognostic factor in breast cancer, with patients having a poorer outcome when HER2-Neu is over-expressed [12]. Our results show better survival among patients with HER2-Neu positive status in HR+ patients, even more prominently among the patients with HR− tumours. In this study, however, HER2-Neu data are missing for the incidence years 2003 and 2004 and, unfortunately, data on the treatment with trastuzumab are lacking. Most studies had limited available data for HER2-Neu status so could not study its prognostic effect [4, 5]. Since 2005 HER2-Neu over-expressed breast cancer patients are treated with adjuvant trastuzumab, the introduction of this anti-HER2-Neu treatment may have neutralized the negative prognostic effect of HER2-Neu over-expression [12].

In our study, age at MBC diagnosis was an independent prognostic factor. Previous studies showed that patients aged <50 years have a better survival after MBC than patients aged >50 years [5, 13]. Thus, although younger women have a higher risk of developing distant metastases than older women, it is a favourable prognostic factor once the metastases have developed. This may be because postmenopausal women receive chemotherapy less often. Additional analyses of our data confirmed this, showing that HR+ patients receiving chemotherapy after MBC diagnosis were significantly younger (data not shown). Moreover, younger patients tend to have a better performance status, and therefore medical specialist tend to offer more treatment options to younger patients.

Previous studies found a relation between the HR status and the site of MBC, with metastases to the bones being more common in HR+ patients and metastases to visceral organs being more common in HR− patients [7, 11, 14, 15]. The present study showed comparable results, with only 13 % of the HR− patients having bone metastases compared to 40 % of the HR+ patients. Multivariable analyses showed that the site of metastasis is an important prognostic factor for survival. Largillier et al. [4] showed that survival for HR+ patients was better than for HR− patients irrespective of the metastatic site, whereas Clark et al. [7] showed that the prognostic effect of HR status

differed according to metastatic site. For example, HR+ patients with bone metastases lived longer than HR− patients with bone metastases. However, these results were based solely on univariable analyses. Although our results showed no significant interaction between metastatic site and HR status, HR− patients with multiple sites may have a more prominent poorer survival compared to patients with bone metastasis, than HR+ patients. This underscores the aggressiveness and explosive growth of the disease for especially HR− patients and the lack of treatment options, such as endocrine treatment, in this subgroup.

As a consequence of the observational design and the lack of detailed information on performance status, co-morbidity and response to primary breast cancer treatment, results for treatment should be interpreted with caution. Still, some interesting results can be commented on. Adjuvant endocrine treatment for primary breast cancer provides a clear contribution to the chances of curing women with an early stage primary breast cancer [16, 17]. Dissemination of primary breast cancer while being treated with adjuvant endocrine treatment is associated with poor survival, probably due to the induction of drug resistance in remaining micro-metastases [17]. Consequently, women with MBC and a HR+ tumour have more treatment options when they have not yet received adjuvant endocrine treatment. This may explain why the HR+ patients with adjuvant endocrine treatment had a poorer survival than the ones without adjuvant endocrine treatment. In contrast to the association with adjuvant endocrine treatment, the use of first-line palliative endocrine treatment was found to have a favourable effect on the overall survival. The role of surgery for MBC remains uncertain, as patients with favourable prognostic factors are more likely to undergo surgical resection. Any comparison with surgically untreated patients will, therefore, be affected by serious biases [18], and our results, showing that surgery is associated with a significantly better survival for patients with MBC, should be interpreted with care. The positive prognostic value of first-line palliative chemotherapy was stronger for HR− patients than for HR+ patients. HR+ patients are often treated with adjuvant or first-line palliative endocrine treatment, which could diminish the effect of first-line palliative chemotherapy. Additional survival analyses showed that first-line palliative chemotherapy for HR− patients gives better survival rates, irrespective of adjuvant chemotherapy. However, for HR+ patients only a positive effect of first-line palliative chemotherapy was seen when patients did not receive adjuvant chemotherapy in patients who develop metastatic disease within 5 years after diagnosis.

While using population-based data from the Netherlands Cancer Registry has the advantage that it is a non-selected large and up-to-date cohort, including all breast cancer patients diagnosed between 2003 and 2006 with recurrent MBC, there are some limitations. Follow-up data were reported for a maximum duration of 5 years after initial treatment, resulting in a more aggressive subgroup with worse survival. In addition, HR status is based on the initial tumour, while breast cancer metastasis may show receptor conversion [19, 20]. Hoefnagel et al. [21] showed that receptor conversion occurred for ER in 10 % and for PR in 30 % of the patients, mainly from positive to negative. These observations introduce a potential bias in our analysis.

Conclusion

The present study underlines the aggressiveness of MBC for HR− patients with a negative HER2-Neu status, a short MFI and multiple metastases. Furthermore, we showed the prognostic value of lymph node status, HER2-Neu status, adjuvant endocrine treatment and first-line palliative chemotherapy depends on HR status. Considering our results, it seems that when first-line palliative treatment options are available at MBC diagnosis and used, MBC patients showed better survival. This knowledge may help physicians to consider individual survival and therapeutic strategies. Further research is needed to assess the effect of different systemic treatment lines on survival in MBC patients.

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Conflict of interest The authors declare that they have no conflict of interest.

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